REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 42, 46-48, 51, 57 and 113-117 are pending and currently under consideration. Applicants thank the Examiner for an informal telephonic discussion of this application with the undersigned representative on November 10, 2004, and for a follow-up voicemail left by the Examiner on November 18, 2004.

REJECTIONS UNDER OBVIOUSNESS TYPE DOUBLE PATENTING

Claims 42, 46-48, 51, 57 and 113-117 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 42 and 46-57 of co-pending U.S. Patent Application No. 09/810,644, and claims 42, 44, 46-51 and 57 of co-pending U.S. Patent Application No. 09/185,904.

Applicants respectfully traverse this provisional basis of rejection and submit that the claims of the three separate applications are each directed to patentably distinct subject matter. In the case of U.S.A.N. 09/810,644 (" '644"), claims 42 and 46-57 have been canceled and the currently pending claims are directed to subject matter that is unquestionably distinct from that encompassed by the claims of the present application, thereby clearly obviating the obviousness-type double patenting rejection over '644 (see the "Appendix: Table of Co-Pending Applications" which was submitted to the PTO in the present application, along with the Preliminary Amendment and Request for Continued Examination, and the Anderson Declaration, on November 3, 2003). Regarding U.S.A.N. 09/185,904 (" '904"), Applicants submit that the instant claims are directed to patentably distinct subject matter. However, solely to expedite prosecution of the present application, Applicants herewith submit a terminal disclaimer with regard to the co-pending '904 application, in compliance with 37 C.F.R. § 1.321. Applicants respectfully request that these provisional rejections be withdrawn.

REJECTION UNDER 35 U.S.C. § 103

Claims 42 and 46 stand rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Cozens et al. (1989 *J. Mol. Biol.* 206(2):261-80) in view of Adrian et al. (1986 *Mol. Cell Biol.* 6(2):626-634). The PTO asserts that at the time of filing the instant application, a person having ordinary skill in the art would have been motivated to express an ANT3 gene of Cozens et al. recombinantly using the method of Adrian et al., in order to produce the ANT3 protein. Additionally, the PTO alleges that Cozens et al. teach expression of the ANT3 polypeptide in several tissues and in HeLa cells, that "HeLa cells represent an isolated pool of ANT3 for which expression studies were performed," and that "the meaning of recombinant provides for the parental recombination of DNA, a[n]d as such, recombinant ANT3 is present in HeLa cells."

Applicants respectfully traverse these grounds of rejection. Briefly, and notwithstanding the assertion in the Action that the PTO has considered Applicants' previous submissions of record, including the Declaration of Dr. Anderson and the Remarks which accompanied the Amendments filed on November 3, 2003, and June 21, 2004, the PTO fails to provide any evidence or reasoning to show that, based on the prior art and in the absence of the teachings of the instant application, at the time of filing a person having ordinary skill in the art could *reasonably have expected successfully* to obtain an isolated recombinant human ANT3 polypeptide that is capable of binding to an ANT ligand and that localizes to a mitochondrial membrane. For reasons previously made of record and as discussed below, Applicants therefore submit that at the time of filing the instant application, a person having ordinary skill in the art would not have been motivated to achieve the presently claimed invention *with the requisite reasonable expectation of success*, given the disclosures of Cozens et al. and Adrian et al., alone or in combination with each other and/or with any other teaching of the prior art.

The present invention is directed to an isolated recombinant human adenine nucleotide translocator (ANT) polypeptide comprising an amino acid sequence of a human ANT3 polypeptide set forth in SEQ ID NO:33, that localizes to a mitochondrial membrane, that is capable of binding an ANT ligand, and that is produced by a method comprising culturing a

host cell comprising a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the ANT polypeptide. In certain further embodiments the host cell lacks an endogenous human ANT1 polypeptide as set forth in SEQ ID NO:31 and also lacks an endogenous human ANT2 polypeptide as set forth in SEQ ID NO:32.

The PTO fails to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. In the current Action, the PTO reiterates its previous reliance, under § 103, on Cozens et al. and Adrian et al., which have also been previously distinguished by Applicants and which, in any event, fail to suggest how successfully to arrive at the presently claimed isolated recombinant human ANT3 polypeptide. The cited publications fail, *inter alia*, to suggest the desirability of using a regulated promoter operably linked to a nucleic acid encoding the ANT3 polypeptide. Contrary to the assertions in the Action, Cozens et al. also fail to demonstrate in several human tissues (liver, muscle, heart, kidney) or in HeLa cells any actual ANT3 *polypeptide*, much less an isolated human ANT 3 polypeptide. Instead, Cozens et al. merely cite a published report (Necklemann et al., 1987 *Proc. Nat. Acad. Sci. USA* 84:7580), which documents northern blot detection of ANT3-encoding mRNA transcripts from these sources, but which fails to provide evidence of actual ANT3 proteins, and which certainly fails to suggest how an ordinarily skilled artisan might reasonably expect successfully to arrive at an *isolated* recombinant human ANT3 *polypeptide* that retains functional properties, as presently claimed.

Adrian et al. merely describe recombinant expression of a β-gal fusion protein containing a truncated yeast ANT polypeptide that comprises a shortened sequence quite distinct from SEQ ID NO:33, in the course of experiments designed to determine whether the truncated polypeptide is delivered to mitochondria. Adrian et al. fail to suggest expressing any recombinant ANT polypeptide using a regulated promoter; Adrian et al. fail to suggest expressing any complete recombinant human ANT polypeptide; Adrian et al. fail to suggest expressing a human ANT3 polypeptide that comprises the amino acid sequence set forth in SEQ ID NO:33; and Adrian et al., alone or in combination with Cozens et al., certainly fail in any way to suggest a reasonable basis upon which a person ordinarily skilled in the art could expect successfully to express a human ANT3 polypeptide using a regulated promoter, where the ANT3 comprises SEQ ID NO:33, localizes to a mitochondrial membrane and is capable of binding an ANT ligand. Applicants therefore disagree with the assertion in the Action that "the ANT3

protein itself is known in the prior art, as taught by Cozens et al.," given that Cozens et al. merely provide deduced ANT3 amino acid sequence *information* but nowhere disclose an isolated ANT3 polypeptide *per se*, and Adrian et al. fail to cure the deficiencies of Cozens et al.

As also noted in Applicants' submissions previously made of record, the relevant art *at the time of filing* recognized, but had not overcome, problems surrounding, *e.g.*, solubilization, denaturation and renaturation of ANT proteins. At the time of filing, a person having ordinary skill in the art could not reasonably have expected successfully to functionally reconstitute an isolated recombinant human ANT3 polypeptide such that it would localize to a mitochondrial membrane and be capable of binding an ANT ligand. In particular, the relevant art fails to suggest or appreciate the importance to recombinant human ANT expression of using a recombinant expression construct that comprises a *regulated promoter*, for purposes of obtaining an ANT polypeptide product that localizes to mitochondrial membranes and that is capable of binding an ANT ligand.

As understood in the art and described in the instant specification (*e.g.*, pages 29-31), a regulated promoter is a promoter that may be treated in some manner so as to increase or decrease expression of an operably linked nucleic acid sequence, for instance, an inducible promoter (*e.g.*, page 29, lines 17-21; page 31, lines 4-18). By contrast, the disclosure of Adrian et al. is limited to the use of a *constitutive* promoter for the expression of fusion proteins having only fragments of ANT polypeptide sequences, which constitutive promoter cannot be a regulated promoter according to the present application. Even several years after the filing date of the instant application, the relevant art failed to appreciate the advantages associated with a regulated promoter and instead continued to seek other solutions to the unsolved problem of recombinant human ANT polypeptide expression, and so was unable to produce isolated human ANT3 polypeptides having the recited functional attributes. As discussed in Applicants' response filed on June 21, 2004, Heimpl et al. (2001) ascribe difficulties in human ANT expression to unfavorable codon utilization, and Hatanaka et al. (2001) attribute problems in expressing human ANT to amino-terminal sequences, but neither of these representative publications from the art several years *after* the instant application filing date suggests how to achieve the invention disclosed in the present application.

It is well settled that for obviousness to be established, both (i) the suggestion of the claimed invention and (ii) the expectation of success must be found in the prior art, and not in Applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016, (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991).

For reasons given herein and in Applicants' previous submissions of record, the PTO fails to explain why it believes the skilled artisan *could reasonably have expected to succeed* in arriving at Applicants' invention when (i) the prior art failed to suggest the desirability of combining the recited elements, (ii) there was a long-felt need in the art to produce the claimed subject matter (*see also* Anderson Declaration), (iii) the prior art tried and failed to achieve Applicants' claimed invention (*see also* Anderson Declaration), and (iv) even the subsequent art failed to overcome the technical difficulties for which Applicants' invention provides a solution. Applicants therefore submit the PTO fails to meet its burden to establish a *prima facie* case of obviousness, in view of the mandatory criteria that both (i) the suggestion of the claimed invention and (ii) the expectation of success must be found in the prior art. *Amgen, Inc. v. Chugai Pharaceutical Co.*, 927 F.2d at 1207-08. See also M.P.E.P. § 2143.02.

Applicants also traverse the PTO's assertions that "HeLa cells represent an isolated pool of ANT3 for which expression studies were performed," and that "the meaning of recombinant provides for the parental recombination of DNA, a[n]d as such, recombinant ANT3 is present in HeLa cells." As disclosed by the instant specification, an "isolated" polypeptide indicates the polypeptide has been removed from its original or natural environment (*e.g.*, page 24, lines 18-19), which would not be the case for an ANT3 polypeptide in an intact HeLa cell (*i.e.*, a HeLa cell that has not been transfected with a recombinant expression construct comprising a regulated promoter operably linked to a nucleic acid encoding the ANT polypeptide, and from which an ANT3 polypeptide having the recited properties of membrane localization and ligand binding has not been removed).

Regarding the meaning of "recombinant," Applicants submit that given the instant application, a person having ordinary skill in the art would not understand either a "recombinant polypeptide" or a "recombinant expression construct" to be the product of "parental recombination of DNA." Applicants understand the PTO's reference to "parental recombination

of DNA" to mean natural genetic recombination events that took place in the reproductive cells which gave rise to the organism from which a somatic tissue sample was obtained and artificially cultured to generate HeLa cells. If this is not the meaning of "parental recombination of DNA" that is intended by the PTO, clarification is respectfully requested. In view of the present specification, which is rife with disclosure pertaining to accepted genetic engineering methodologies commonly referred to by persons having ordinary skill in the art as "recombinant" methods, for instance recombinant genetic techniques or recombinant DNA technology, Applicants submit that it is clear that neither the presently recited "recombinant polypeptide" nor the presently recited "recombinant expression construct" refers to a product of a natural "parental recombination of DNA." Accordingly, and contrary to the allegation made by the PTO, absent any artificial molecular genetic manipulations taught by the instant application, an intact cell of the well known HeLa cell line does not comprise an isolated recombinant human ANT3 polypeptide of the present invention.

The U.S. Supreme Court has held that objective evidence of "secondary considerations," including "long felt but unsolved needs, [and] failure of others" must be factored into the examination of an application for purposes of determining the nonobviousness of an invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). See also *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). The Federal Circuit has held that secondary considerations are "invariably relevant" to the test of obviousness. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1575, 42 U.S.P.Q.2d 1378, 1381 (Fed. Cir. 1997). Applicants have presented evidence of such secondary considerations in the previously submitted Declaration under 37 C.F.R. § 1.132 of Dr. Christen Anderson (submitted November 3, 2003).

The PTO asserts that the Anderson Declaration has been considered, but the PTO has provided no express comment on the evidence provided in the Declaration, in particular, evidence of the long-felt but unsolved need in the art for isolated functional human ANT3 polypeptides, and evidence of the failure of others to achieve Applicants' invention, despite the availability for nearly a decade prior to Applicants' filing date of the ANT3 coding sequence and of recombinant expression methodologies. The PTO fails to provide any rationale for its

rejection of Applicants' arguments *in toto* as "not persuasive." In view of arguments presented here and those previously made of record, and specifically in view of Applicants' argument that the PTO has failed to show why a person having ordinary skill in the art at the time of filing *could reasonably have expected successfully* to arrive at the claimed invention, Applicants respectfully request that the PTO reconsider the Anderson Declaration.

Further to the Examiner's informal telephonic discussion of this application with the undersigned representative on November 10, 2004, and to the follow-up voicemail left by the Examiner on November 18, 2004, Applicants thank the PTO for reviewing Applicants' previous submissions of record. Applicants submit, however, that the PTO fails to establish a *prima facie* case of obviousness in its allegation that references of record anticipate the claimed invention. The PTO has not met its burden of showing why a person having ordinary skill in the art would have had the *required* reasonable expectation of successfully practicing the invention, absent the present application.

It is well settled that an invention which is claimed as a product-by-process is not obvious where an applicant presents evidence showing non-obvious differences between the claimed invention and the prior art. See M.P.E.P. §§ 2113 and 2173.05(p). With respect to the instant claims, Applicants have provided such evidence in the aforementioned Declaration, in the specification (*e.g.*, at page 82, lines 19-25; page 114, line 30 through page 115, line 11; page 119, line 12 through page 120, line 2) and in the Drawings. Specifically, Applicants have demonstrated that the claimed recombinant human ANT3 polypeptide (comprising SEQ ID NO:33) is capable of being produced recombinantly in a manner such that it localizes to a mitochondrial membrane *and* is capable of binding an ANT ligand, features which reflect non-obvious differences between the claimed invention and the prior art, for reasons given above.

Moreover, and as noted above, for obviousness to be established, *both* (i) the suggestion of the claimed invention *and* (ii) the expectation of success must be found in the prior art. Thus, even assuming, solely for argument's sake, that a suggestion of the invention might be found in the art, the PTO still fails to establish *prima facie* obviousness because the prior art fails to provide the ordinarily skilled artisan with any reasonable expectation whatsoever of successfully arriving at the invention. In particular, the prior art fails to provide the requisite

expectation of successfully arriving at a human ANT3 polypeptide *that is capable of being produced recombinantly* such that it possesses the recited properties, *i.e.*, a *recombinant* human ANT3 polypeptide. Indeed, the prior art is if anything rife with failure, as observed in the Anderson Declaration, while it is a reasonable expectation of success that is a required element for establishing obviousness. Applicants therefore submit that the obviousness rejection cannot be maintained where, as here, the PTO fails to provide any evidence or reasoning to show that the required element of a reasonable expectation of success can be found in the prior art.

In view of the foregoing, including the Remarks provided herein and evidence previously made of record, Applicants respectfully submit the presently claimed invention meets the requirements of 35 U.S.C. §103(a) and request withdrawal of these rejections.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 117 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the PTO alleges that the instant specification does not convey to a person skilled in the art that the inventors possessed an embodiment of ANT3 wherein one and only one amino acid has been substituted.

Applicants respectfully traverse this rejection and submit the application satisfies the written description requirement of 35 U.S.C. §112, first paragraph. As disclosed in the specification and recited in the claims, the instant invention is directed to an isolated recombinant human ANT polypeptide comprising the sequence set forth in SEQ ID NO: 33, that localizes to a mitochondrial membrane, that is capable of binding an ANT ligand, and that is produced by a method comprising culturing a host cell comprising a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the ANT polypeptide, in which one amino acid is substituted.

The specification describes the claimed invention in sufficient detail and in full, clear, concise and exact terms such that one skilled in the art can reasonably conclude Applicants had possession of the invention at the time of filing the application. Specifically, the

specification teaches that ANT3 variant polypeptides, such as the instant ANT polypeptide in which one amino acid is substituted (*e.g.*, page 23, lines 14-16), retain essentially the same biological function or activity (*e.g.*, binding to an ANT ligand or localizing to a mitochondrial membrane) as the unsubstituted ANT polypeptide (*e.g.*, page 23, lines 3-7). The specification also discloses that ANT variants according to the invention may be encoded by nucleic acid molecules comprising nucleotide substitutions that give rise to amino acid substitutions which do not substantially alter the function of the encoded ANT polypeptide (*e.g.*, page 21, lines 6-11).

As provided by the specification and known to the art, a number of established methodologies may be employed to make an ANT polypeptide in which one amino acid is substituted (*e.g.*, page 21, line 18 through page 22, line 8). Moreover, throughout the specification, including in the Examples, there are provided multiple teachings from which the skilled person can readily determine whether a given recombinant human ANT3 polypeptide having one amino acid that is substituted (i) localizes to a mitochondrial membrane and (ii) is capable of binding an ANT ligand.

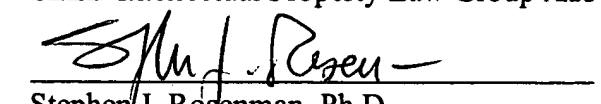
Accordingly, given the instant specification, a person skilled in the art would readily appreciate that Applicants were in possession of the invention at the time the application was filed. The requirements of the written description requirement under 35 U.S.C. § 112, first paragraph are clearly satisfied, and withdrawal of this rejection is respectfully requested.

Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of the case, the Examiner is invited to telephone the undersigned representative at (206) 622-4900.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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